

Attorney Docket No.: DEX-0253
Inventors: Sun et al.
Serial No.: 10/016,157
Filing Date: October 31, 2001
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Amendments to the Specification:

Please replace the paragraph at page 54, lines 12 through 28 with the following:

Polypeptides of the invention may be post-translationally modified. Post-translational modifications include phosphorylation of amino acid residues serine, threonine and/or tyrosine, N-linked and/or O-linked glycosylation, methylation, acetylation, prenylation, methylation, acetylation, arginylation, ubiquitination and racemization. One may determine whether a polypeptide of the invention is likely to be post-translationally modified by analyzing the sequence of the polypeptide to determine if there are peptide motifs indicative of sites for post-translational modification. There are a number of computer programs that permit prediction of post-translational modifications. See, e.g., ~~www.expasy.org (accessed August 31, 2001)~~ expasy.org of the world wide web, which includes PSORT, for prediction of protein sorting signals and localization sites, SignalP, for prediction of signal peptide cleavage sites, MITOPROT and Predotar, for prediction of mitochondrial targeting sequences, NetOGlyc, for prediction of type O-glycosylation sites in mammalian proteins, big-PI Predictor and DGPI, for prediction

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of prenylation-anchor and cleavage sites, and NetPhos, for prediction of Ser, Thr and Tyr phosphorylation sites in eukaryotic proteins. Other computer programs, such as those included in GCG, also may be used to determine post-translational modification peptide motifs.

Please replace the paragraph at page 54, line 29 through page 55, line 8 with the following:

General examples of types of post-translational modifications may be found in web sites on the world wide web such as the Delta Mass database ~~http://www.abrf.org/ABRF/Research Committees/deltamass/deltamass.html (accessed October 19, 2001)~~ abrf.org/ABRF/Research Committees/deltamass/deltamass.html; "GlycoSuiteDB: a new curated relational database of glycoprotein glycan structures and their biological sources" Cooper et al. Nucleic Acids Res. 29; 332-335 (2001) and ~~http://www.glycosuite.com/ (accessed October 19, 2001)~~ glycosuite.com; "O-GLYCBASE version 4.0: a revised database of O-glycosylated proteins" Gupta et al. Nucleic Acids Research, 27: 370-372 (1999) and ~~http://www.cbs.dtu.dk/databases/OGLYCBASE/ (accessed October 19, 2001)~~ cbs.dtu.dk/databases/OGLYCBASE/;

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"PhosphoBase, a database of phosphorylation sites: release 2.0.",
Kreegipuu et al. Nucleic Acids Res 27(1):237-239 (1999) and
~~http://www.cbs.dtu.dk/databases/PhosphoBase/ (accessed October~~
~~19, 2001) cbs.dtu.dk/databases/PhosphoBase/; or~~
~~http://pir.georgetown.edu/pirwww/search/textresid.html (accessed~~
~~October 19, 2001) pir.georgetown.edu/pirwww/search~~
~~/textresid.html.~~

Please replace the paragraph at page 57, lines 1 through 22
with the following:

In another embodiment, the invention provides polypeptides
that have been post-translationally modified. In one embodiment,
polypeptides may be modified enzymatically or chemically, by
addition or removal of a post-translational modification. For
example, a polypeptide may be glycosylated or deglycosylated
enzymatically. Similarly, polypeptides may be phosphorylated
using a purified kinase, such as a MAP kinase (e.g, p38, ERK, or
JNK) or a tyrosine kinase (e.g., Src or erbB2). A polypeptide
may also be modified through synthetic chemistry. Alternatively,
one may isolate the polypeptide of interest from a cell or tissue
that expresses the polypeptide with the desired post-

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translational modification. In another embodiment, a nucleic acid molecule encoding the polypeptide of interest is introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide in the desired fashion. If the polypeptide does not contain a motif for a desired post-translational modification, one may alter the post-translational modification by mutating the nucleic acid sequence of a nucleic acid molecule encoding the polypeptide so that it contains a site for the desired post-translational modification. Amino acid sequences that may be post-translationally modified are known in the art. See, e.g., the programs described above on the website ~~www.expasy.org~~ expasy.org of the world wide web. The nucleic acid molecule is then be introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide. Similarly, one may delete sites that are post-translationally modified by either mutating the nucleic acid sequence so that the encoded polypeptide does not contain the post-translational modification motif, or by introducing the native nucleic acid molecule into a host cell that is not capable of post-translationally modifying the encoded polypeptide.

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Please replace the paragraph at page 59, line 29 through page 60, line 10, with the following:

Plasmid vectors will typically be introduced into chemically competent or electrocompetent bacterial cells. *E. coli* cells can be rendered chemically competent by treatment, e.g., with CaCl_2 , or a solution of Mg^{2+} , Mn^{2+} , Ca^{2+} , Rb^+ or K^+ , dimethyl sulfoxide, dithiothreitol, and hexamine cobalt (III), Hanahan, *J. Mol. Biol.* 166(4):557-80 (1983), and vectors introduced by heat shock. A wide variety of chemically competent strains are also available commercially (e.g., Epicurian Coli® XL10-Gold® Ultracompetent Cells (Stratagene, La Jolla, CA, USA); DH5α competent cells (Clontech Laboratories, Palo Alto, CA, USA); and TOP10 Chemically Competent *E. coli* Kit (Invitrogen, Carlsbad, CA, USA)). Bacterial cells can be rendered electrocompetent, that is, competent to take up exogenous DNA by electroporation, by various pre-pulse treatments; vectors are introduced by electroporation followed by subsequent outgrowth in selected media. An extensive series of protocols is provided online via the world wide web in Electroprotocols (BioRad, Richmond, CA, USA) (http://www.biorad.com/LifeScience/pdf/New_Gene_Pulser.pdf http://www.biorad.com/LifeScience/pdf/New_Gene_Pulser.pdf).

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Please replace the paragraph at page 61, lines 1 through 18 with the following:

Mammalian and insect cells can be directly infected by packaged viral vectors, or transfected by chemical or electrical means. For chemical transfection, DNA can be coprecipitated with CaPO_4 or introduced using liposomal and nonliposomal lipid-based agents. Commercial kits are available for CaPO_4 transfection (CalPhos™ Mammalian Transfection Kit, Clontech Laboratories, Palo Alto, CA, USA), and lipid-mediated transfection can be practiced using commercial reagents, such as LIPOFECTAMINE™ 2000, LIPOFECTAMINE™ Reagent, CELLFECTIN® Reagent, and LIPOFECTIN® Reagent (Invitrogen, Carlsbad, CA, USA), DOTAP Liposomal Transfection Reagent, FuGENE 6, X-tremeGENE Q2, DOSPER, (Roche Molecular Biochemicals, Indianapolis, IN USA), Effectene™, PolyFect®, Superfect® (Qiagen, Inc., Valencia, CA, USA). Protocols for electroporating mammalian cells can be found online via the world wide web in Electroprotocols (Bio-Rad, Richmond, CA, USA) (~~[http://www.bio-rad.com/LifeScience/pdf/](http://www.bio-rad.com/LifeScience/pdf/New_Gene_Pulser.pdf)~~~~[New_Gene_Pulser.pdf](http://www.bio-rad.com/LifeScience/pdf/New_Gene_Pulser.pdf)~~ ~~[bio-rad.com/ LifeScience/pdf/](http://www.bio-rad.com/LifeScience/pdf/New_Gene_Pulser.pdf)~~~~[New_Gene_Pulser.pdf](http://www.bio-rad.com/LifeScience/pdf/New_Gene_Pulser.pdf)~~); Norton et al. (eds.), Gene Transfer Methods: Introducing DNA into Living Cells and Organisms,

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BioTechniques Books, Eaton Publishing Co. (2000); incorporated herein by reference in its entirety. Other transfection techniques include transfection by particle bombardment and microinjection. See, e.g., Cheng et al., *Proc. Natl. Acad. Sci. USA* 90(10): 4455-9 (1993); Yang et al., *Proc. Natl. Acad. Sci. USA* 87(24): 9568-72 (1990).

Please replace the paragraph at page 129, lines 5 through 12 with the following:

Examples of post-translational modifications (PTMs) of the BSPs of this invention are listed below. In addition, antibodies that specifically bind such post-translational modifications may be useful as a diagnostic or as therapeutic. Using the ProSite database (Bairoch et al., *Nucleic Acids Res.* 25(1):217-221 (1997), the contents of which are incorporated by reference), the following PTMs were predicted for the LSPs of the invention using the world wide web (~~http://npsa-pbil.ibcp.fr/cgi-bin/npsa_automat.pl?page=npsa_prosite.html~~ most recently accessed October 23, 2001 http://npsa-pbil.ibcp.fr/cgi-bin/npsa_automat.pl?page=npsa_prosite.html most recently accessed October 23, 2001). For full definitions of the PTMs see ~~http://www.expasy.org/cgi-bin/prosite-list.pl~~ most recently

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~~accessed October 23, 2001 expasy.org/cgi-bin/prosite-list.pl on~~
~~the world wide web.~~